REMARKS

With this Response, claims 1, 5-11, 24 and 28-32 are canceled. In addition, claims 12 and 33 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

The January 11, 2005 Final Office Action objected to claim 5 because claim 5 depends from canceled claim 3. With this Response, claim 5 has been canceled. As such, the objection to claim 5 has been obviated.

In summary, the claims of the present application were found obvious over a primary reference (Xue et al.) which discloses a device capable of separating anions of a sample from cations of a sample, in view of a secondary reference (Karger et al.) which discloses a capillary comprising a coating wherein the coating reduces an electroosmotic charge of the capillary. With this Response, the Applicant has canceled a number of claims and amended all pending independent claims to specifically recite a microfluidic (as opposed to a capillary) apparatus wherein the columns have been coated with an amount of a coating to substantially eliminate sample loss. As will be explained below, the elimination of sample loss is a key improvement in the field of microfluidic technology because such an improvement allows for the use of a smaller starting sample and as such, a more efficient device and process. Loss of a small amount of a sample is of less concern to a device utilizing a capillary system because such capillary systems use much larger amounts of starting material as compared to a microfluidic system. The cited references do not address the issue of sample loss; therefore, the cited references do not disclose or suggest a device or method wherein the columns have been coated with an amount of a coating to substantially eliminate sample loss.

Applicant believes that the current claim cancellations and amendments clearly overcome the cited 35 U.S.C. §103(a) rejections; as such, Applicant respectfully requests reconsideration and allowance of pending claims 12, 14, 18-23, 33, 37-41 and 43.

Claims Rejected Under 35 U.S.C. §103(a):

The January 11, 2005 Office Action rejected all pending under 35 U.S.C. §103(a) as being unpatentable over various combinations of Xue et al., Karger et al, Lee et al. and Kopf-Sill et al.

As summarized in the Office Action, the Xue et al. reference discloses:

> Relevant to claims 1 and 12, Xue et al disclose a microfluidic bi-directional capillary electrophoresis device (Figure 7b), comprising: a middle column (24 and 25), the middle column intersecting a first channel and a second channel (26 and 27) at a point wherein the middle column is approximately perpendicular to the first and second channels (23), a negative electrode in communication with the first channel and a positive electrode in communication with the second channel (33), wherein a mixture of anions and cations may be separated by drawing them towards the electrodes of opposite polarity.
>
> Relevant to claims 24 and 33, Xue et al disclose a method of separating a sample of anions and cations in a microfluidic capillary system, comprising: delivering the sample to the middle column of the device described above in addressing claims 1 and 12 (Paragraph 0071 – sample in 28 and vacuum applied to 29 would lead to sample traveling through channels 24 and 25), positioning negative and positive electrodes (33) in communication with the first and second channels, thereby drawing anions and cations into the channel corresponding to the electrode of opposite polarity (Paragraph 0071, Figure 9).
>
> ...
>
> **Xue et al do not explicitly disclose a coated first channel, a coated second channel, or a first channel engaged to a microfluidic system for proteome analysis (Claims 1, 12, 24, and 33); a first channel coated with Triton X-100 (Claims 5, 18, 28, and 37); or a second channel engaged to a second microfluidic system for proteome analysis (Claims 14 and 43).** (January 11, 2005 Office Action; Pages 4-5)(Emphasis added).

According to the Office Action, the Karger et al. reference discloses:

> Relevant to claims 1, 12, 24, and 33, Karger et al disclose **capillary channels that have been coated with Triton X-100 in order to reduce electroosmosis in electrophoretic separations (Column 5, lines 3-39).** (January 11, 2005 Office Action; Page 5)(Emphasis added).

Regarding combining the Xue et al. reference with the Karger et al. reference under 35 U.S.C. §103(a), the Office Action states:

> It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the devices and methods of Xue et al by coating the first and second channels (26 and 27) with Triton X-100, as taught by Karger et al, **because it would reduce electroosmosis. Such coatings would be an obvious modification of the devices and methods of Xue et al, because it would be desirable to minimize electroosmosis in such a system, wherein oppositely charged analytes migrate in opposite directions within a channel. Excessive electroosmosis would lead to a bulk flow that prevents migration in one of the directions, or leads to undesirably long migration times, as would be obvious to one having ordinary skill in the art...**(January 11, 2005 Office Action; Pages 5-6)(Emphasis added).

With this Amendment, Applicant has amended independent claims 12 and 33 so that these claims specifically requires a microfluidic device where the coating of the first channel and the coating of the second channel are each applied in a amount to substantially eliminate sample loss. Due to the extremely small amount of sample used in a microfluidic process, a device or method which has been optimized to substantially eliminate sample loss is a great benefit to the field of microfluidics. The Karger et al. reference does not disclose or suggest the benefits of preventing sample loss in a microfluidic process; the Karger et al. reference merely discloses a method of reducing eletroosmosis in a capillary system. As such, in the current Response, the Applicant has amended the claims (and canceled several claims) in order to overcome the current rejections and to present an optimized microfluidic device wherein the channels have been coated in order to substantially eliminate sample loss.

As stated above, independent claims 12 and 33 have been amended to recite a microfluidic device having a middle column intersecting a first uncharged channel having a coating and a second uncharged channel having a coating at an intersection point wherein the coating of the first column and the coating of the second column are applied in an amount to substantially eliminate sample loss. Support for these amendments can be found throughout the specification as filed. More specifically, the specification discloses:

> In one aspect of the present invention, the uncharged capillary or column allows for minimal interaction between the sample and the walls of the capillary or column. **The minimal interaction between the sample and the uncharged capillary or column allows for minimal sample loss.** (Specification; Page 3, Line 27-Page 4, Line 3)(Emphasis added).
>
> ...In one aspect of the present invention, a low or no EOF is used with the coating of capillaries and microchannels to **minimize analyte adsorption to the capillary walls**. The generation of electroosmotic flow requires the presence of ionizable groups on the surface of the capillary or the microchannel walls. **However, these ionizable groups also lead to unwanted charge based interactions that can lead to sample loss and peak broadening**...(Specification; Page 4, Lines 12-17)(Emphasis added).
>
> ...An uncharged capillary or column allows for less interaction between the analytes and the column. Biological samples, such as but not limited to polypeptides, have many unwanted ionic interactions with the surface of the capillary column. **As such, less analytes are lost during the procedure allowing the user to begin with a smaller amount of sample to be separated than has been customarily used in connection with the prior art**...(Specification; Page 5, Lines 11-16)(Emphasis added).
>
> ...The use of low or no EOF is of increasing importance as advancements are being made in the coating of capillaries and microchannels to minimize analyte adsorption to the capillary walls. The generation of electroosmotic flow requires the presence of ionizable groups on the surface of the capillary or the microchannel walls. **However, these ionizable groups also lead to unwanted charge based interactions that can lead to sample loss and peak broadening. Minimizing or negating charge interactions at the wall/solution (solid/liquid) interface is necessary to avoid these interactions**...(Specification; Page 7, Lines 8-14)(Emphasis added).
>
> **...As such, less analytes are lost during the procedure allowing the user to begin with a smaller amount of sample to be separated than has been customarily used in connection with the prior art...**(Specification; Page 7, Lines 24-26)(Emphasis added).

As amended, the claims of the present application recite a microfluidic device wherein a coating has been applied to a first column and to a second column of the microfluidic device. The application of the coating results in the elimination of electroosmotic flow through each column; further, the coatings are applied in an amount wherein sample loss is substantially eliminated. As will be discussed below, the cited references do not disclose or suggest a microfluidic device

wherein the channels have been coated in an amount to substantially reduce sample loss. As such, Applicant respectfully request reconsideration and allowance of pending claims 12, 14. 18-23, 33, 37-41 and 43.

As stated by the Office Action, the Xue et al. reference discloses a microfluidic bi-directional capillary electrophoresis device, comprising: a middle column, the middle column intersecting a first channel and a second channel at a point wherein the middle column is approximately perpendicular to the first and second channels, a negative electrode in communication with the first channel and a positive electrode in communication with the second channel, wherein a mixture of anions and cations may be separated by drawing them towards the electrodes of opposite polarity. However, the Xue et al. reference does not disclose or suggest the use a coating on the columns of the device. Further, the Xue et al. reference does not mention or suggest any solutions to the problem of preventing sample loss in a microfluidic device.

The Karger et al. reference is cited by the Office Action as a cure for the above-mentioned deficiency of the Xue et al. reference. More specifically, the Office Action states that the Karger et al. reference discloses a capillary column comprising a coating wherein the coating substantially eliminates electroosmotic flow. However, the Karger et al. reference does not disclose, teach or suggest the optimization of a microfluidic device wherein various columns of the microfluidic device comprise a coating in an amount which substantially eliminates sample loss.

More specifically, the Karger et al. reference discloses:

> **The improved capillary columns of the invention which contain an improved coating matrix are extremely versatile and eliminate the effects of electroosmosis and other surface zeta potential electrophoresis associated phenomena under a variety of electrophoretic conditions.** The exceptional stability of the coating matrix enables the column to withstand repeated uses including having an polymeric gel filling pushed out of the column and replaced numerous times without the need for reapplying the coating. **The coating further stabilizes the column under relatively harsh electrophoretic conditions such as high temperatures and weak buffers. Most importantly, the**

> **improved capillary columns of the invention can be operated in high electric fields (or at high power), without the breakdown of the coating and changes in the effects of electroosmosis as has been a major problem in the past**. Therefore, the columns of the invention permit high resolution separations to be achieved in a short period of time.
>
> **The coating matrix of the invention can also be used to form a highly stable, hydrophilic coating matrix on the internal and external surfaces of alkyl-bonded, porous silica particles used for high performance liquid chromatography (HPLC)**. It can also be used on porous HPLC particles containing polystyrene. (Karger et al.; Col. 7, Line 62-Col. 8, Line 12)(Emphasis added).

A primary benefit of the use of a microfluidic device over using a prior art capillary based analysis is the ability to utilize extremely small sample sizes. The use of a small sample size allows for a large number of samples to be analyzed in parallel. As such, the ability to utilize a smaller sample size, without the fear of sample loss, is a large and beneficial improvement in the field of microfluidic technology. The Karger et al. reference does not teach, suggest or disclose any type of microfluidic device. The Karger et al. reference merely discloses an improvement of the ability of a capillary column to perform capillary gel electrophoresis. The Karger et al. reference is not concerned with preventing sample loss in a microfluidic device. As such, Applicant respectfully requests reconsideration and allowance of pending claims 12, 14. 18-23, 33, 37-41 and 43.

The Office Action further cited the Lee et al. reference and the Kopf-Sill et al. reference. These references were cited to cure various deficiencies of the Xue et al. in view of the Karger et al. reference. However, neither the Lee et al. reference nor the Kopf-Sill et al. reference, alone or in any combination, disclose, teach or suggest a microfluidic device wherein the columns have been treated with a coating to eliminate electroosmotic flow and to substantially eliminate sample loss. As such, Applicant respectfully requests reconsideration and allowance of pending claims 12, 14. 18-23, 33, 37-41 and 43.

With this Amendment, Applicant has made an earnest effort to respond to all issues raised in the Office Action of January 11, 2005, and to place all claims presented in condition for allowance. No amendment made was for the purpose of narrowing the scope of any claim,

unless Applicant has argued herein that such amendment was made to distinguish over a particular reference or combination of references.

Applicant submits that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicant respectfully requests the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

Date: April 11, 2005

Name: Michael P. Doyle
Registration No.: 49,052
Customer No.: 29932
Palmer & Dodge LLP
111 Huntington Avenue
Boston, MA 02199-7613
Tel.: (617) 239-0100